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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/028,075	12/21/2001	Nisar Asmed Khan	2183-5223US	1102
24247	7590	06/04/2007		
TRASK BRITT P.O. BOX 2550 SALT LAKE CITY, UT 84110			EXAMINER DUNSTON, JENNIFER ANN	
			ART UNIT	PAPER NUMBER
			1636	
			MAIL DATE	DELIVERY MODE
			06/04/2007	PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.



Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :2/21/2002, 10/15/2002, 1/9/2004, 5/13/2004, 6/30/2006, 9/29/2006, 11/9/2006, 12/11/2006.

## DETAILED ACTION

### *Continued Examination Under 37 CFR 1.114*

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6/30/2006 has been entered.

Receipt is acknowledged of an amendment, filed 6/30/2006, in which claims 1 and 5 were amended. Receipt is also acknowledged of an amendment, filed 11/9/2006 in which claim 19 was amended. Currently, claims 1-22 are pending.

### *Election/Restrictions*

Applicant elected Group I (claims 1-5) without traverse in the response filed 10/28/2003. Upon further consideration, the restriction requirement between Groups I and III has been withdrawn.

Claims 6-8 and 11-22 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 10/28/03.

Currently, claims 1-5 and 9-10 are under consideration.

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***Priority***

Acknowledgment is made of applicant's claim for foreign priority based on an application 01203748.7 filed in the European Patent Office on 10/4/2001. It is noted, however, that applicant has not filed a certified copy of the 01203748.7 application as required by 35 U.S.C. 119(b).

***Information Disclosure Statement***

Receipt of information disclosure statements, filed on 2/21/2002, 10/15/2002, 1/9/2004, 5/13/2004, 6/30/2006, 9/29/2006, 11/9/2006 and 12/11/2006, is acknowledged. The signed and initialed PTO 1449s have been mailed with this action.

***Specification***

The substitute specification filed 3/7/2007 has been entered.

The use of the trademarks VYDAC (paragraph [00128]), PREGNYL (paragraphs [00132], [00134] and [00170]), COULTER COUNTER (paragraph [00145]), BAYTRIL (paragraphs [00112], [00261], [00267], [00272], [00273] and [00274]), and GENECHIP (paragraph [00034], [00035], [00275] and [00276]) has been noted in this application. The trademarks should be capitalized wherever they appear and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

### ***Claim Objections***

Claim 3 is objected to because of the following informalities: the term “comprises” is an open-ended transitional phrase; however, it is clear that the claim is limiting the naturally occurring polypeptide to human chorionic gonadotropic hormone. It would be remedial to replace the phrase “comprises human chorionic gonadotropic hormone” with the phrase “is human chorionic gonadotropic hormone.” Appropriate correction is required.

Claim 4 is objected to because of the following informalities: the term “comprises” is an open-ended transitional phrase; however, it is clear that the claim is limiting the cell to a eukaryotic cell. It would be remedial to replace the phrase “comprises an eukaryotic cell” with “is an eukaryotic cell.” Appropriate correction is required.

Claim 10 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 10 is drawn to the method of claim 9 further comprising the step of “determining relative up-regulation and/or down-regulation of at least one gene expressed in said cell.” However, this method step is present in claim 9. Thus, claim 10 does not add any additional method steps or limitations to claim 9.

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

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Claims 1-5, 9 and 10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This is a new rejection.

Claim 1 is vague and indefinite in that the metes and bounds of the claimed method are unclear. The preamble recites “a method for obtaining information about the capacity or tendency of an oligopeptide of at most 9 amino acids long to regulate expression of a gene”. However, it is not clear that determining the presence of NF-kappaB/Rel protein in or derived from a cell contacted with the oligopeptide will *necessarily* result in determining the ability of the oligopeptide to regulate the expression of a gene or a NF-kappaB/Rel gene. Detecting the presence of a protein does not require one to determine the quantity of protein present, and the claims do not require a comparison of the quantity of protein present in the presence and absence of the oligopeptide. Therefore, it is unclear if one necessarily accomplishes what is intended for the method by practicing the recited method step(s).

Claims 2-5 depend from claim 1 and thus are indefinite for the same reasons as applied to claim 1.

Claim 5 is vague and indefinite in that the metes and bounds of the phrase “determining the ratio of said NF-kappaB/Rel protein found in step b) to gene product found in step c)” are unclear. The phrase is unclear in that claim 5 recites the limitation “gene product” in line 4. There is insufficient antecedent basis for this limitation in the claim. Given the broadest reasonable interpretation, the term “gene product” can be interpreted to mean both messenger RNA and protein (e.g., paragraphs [0034] and [00275] of the instant specification). Thus, it is unclear what is being compared. Furthermore, the claims do not require a quantitative analysis

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of NF-kappaB/Rel protein present in or derived from the cell. Determining the presence of a protein only requires the determination of categorical data (e.g., presence vs. absence).

Accordingly, it is unclear how one determines the claimed ratio.

Claim 9 is vague and indefinite in that the metes and bounds of the phrase “relative up-regulation and/or down-regulation of at least one gene” are unclear. The phrase is unclear in that any one gene can only be up-regulated or down-regulated, either the gene expression increases or decreases. It is unclear if the measurement of up- and down-regulation applies only when multiple genes are tested or whether the claim intends to measure the up- and down-regulation of a single gene. It would be remedial to amend the claim to replace the term “up-regulation and/or down regulation” with the term “up-regulation or down-regulation.”

Claim 10 is vague and indefinite in that the metes and bounds of the phrase “relative up-regulation and/or down-regulation of at least one gene” are unclear. The phrase is unclear in that any one gene can only be up-regulated or down-regulated, either the gene expression increases or decreases. It is unclear if the measurement of up- and down-regulation applies only when multiple genes are tested or whether the claim intends to measure the up- and down-regulation of a single gene. It would be remedial to amend the claim to replace the term “up-regulation and/or down regulation” with the term “up-regulation or down-regulation.”

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.



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Claims 1-5 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for identifying an oligopeptide that is capable of regulating the expression of a gene, comprising (a) contacting a cell with said oligopeptide, (b) determining the amount of NF-kappaB/Rel protein in said cell, (c) determining the amount of NF-kappaB/Rel protein in a cell that has not been contacted with said oligopeptide, and (d) determining the ratio of said amount of NF-kappaB/Rel protein found in step (b) to the amount of NF-kappaB/Rel protein found in step (c), does not reasonably provide enablement for methods of determining the ability of an oligopeptide to regulate gene expression where only the presence of NF-kappaB is determined and where the level of NF-kappaB is not compared to a control. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

*Nature of the invention:* The claims are drawn to a method for obtaining information about the capacity or tendency of an oligopeptide of at most 9 amino acids long to regulate expression of a gene. However, the claims only require the step of determining the presence of a NF-kappaB/Rel protein in or derived from a cell that has been contacted with the oligopeptide. Given the broadest reasonable interpretation, the determination of the presence of NF-kappaB/Rel protein does not require a quantitative determination of the amount of NF-kappaB

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protein in or derived from the cell. Determining the presence of the protein only requires a qualitative assessment of the presence or absence of the protein. Thus, the nature of the invention is complex, because one must be capable of determining the ability of the peptide to change the level of expression of a gene by looking at the presence or absence of NF-kappaB/Rel protein in a cell contacted with a peptide. The method does not provide a reference for one to determine whether any up-regulation or down-regulation of any gene expression has occurred. With respect to claim 5, the method does not necessarily provide data for NF-kappaB/Rel protein that one could use to determine a ratio.

*Breadth of the claims:* The claims are broad in that the method encompasses any method of determining the presence of an NF-kappaB/Rel protein, including qualitative methods. Further, the claims are broad in that the regulation of expression is not determined by a specific comparison of two experimental conditions (i.e., the presence and absence of the oligopeptide). The complex nature of the subject matter of this invention is exacerbated by the breadth of the claims.

*Guidance of the specification and existence of working examples:* The specification envisions method to determine whether small oligopeptides act as signaling molecules to allow for improved bioavailability of the signaling molecule (e.g., paragraph [0032]). The specification envisions a method comprising the steps of (a) contacting the oligopeptide, or a modification or derivative thereof, with at least one cell, and (b) determining the presence of at least one gene product in or derived from the cell (e.g., paragraph [0033]). The specification teaches that the method may further comprise the step of determining the presence of the gene product in or derived from a cell that has not been contacted with the oligopeptide, or a

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modification or derivative thereof, and determining the ratio of the gene product found in the presence of the oligopeptide to the absence of the oligopeptide (e.g., paragraph [0034]). The specification envisions determining the up-regulation and/or down-regulation of at least one gene using methods such as Northern or Western blotting or nucleic acid detection by PCR or immunological detection of proteins (e.g., paragraph [0035]). Up-regulation of a gene product is when a cell makes more mRNA or protein, whereas down-regulation of a gene produce is when a cell makes less mRNA or protein (e.g., paragraph [0035]). The specification teaches that NF-kappaB/Rel protein is a preferred gene of which to determine the regulation of expression (e.g., paragraph [0038]). The working examples of the specification demonstrate that the amount of NF- $\kappa$ B protein can be determined using an electrophoretic mobility shift assay (EMSA) (e.g., paragraph [00127]; Figure 31).

*Predictability and state of the art:* The claims are drawn to a method of obtaining information about the capacity or tendency of an oligopeptide to regulate the expression of a gene. In essence, the method tests the hypothesis that a test oligopeptide will have an effect on the expression of a gene. It is well known in the art that to test a hypothesis, the experiments must be controlled. Control experiments are of vital importance, since only a controlled test has any hope of illuminating anything (Keeton and Gould. Biological Science, 5<sup>th</sup> Ed. New York: W.W. Norton & Company, Inc., 1993, page 4). When determining whether a particular oligopeptide alters the expression of NF-kappaB/Rel protein, the prior art teaches the inclusion of a control that has not been contacted with the oligopeptide such that one can determine if the oligopeptide induces a change (e.g., Ichiyama et al. Brain Research, Vol. 836, pages 31-37, 1999, Figure 3; Han et al. American Journal of Physiology, Vol. 277, pages C74-C82, July 1999,

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page C75, Pancreatic acini isolation and treatments, and Figures 1-2). Thus, it would be unpredictable to draw any conclusions about the capacity or tendency of an oligopeptide to regulate the expression of a gene without including a control that is a cell that has not been contacted with the peptide.

*Amount of experimentation necessary:* The quantity of experimentation is large, as one could carry out the claimed method steps without ever determining whether the oligopeptide has the capacity or tendency to regulate gene expression. Thus, one would be required to determine the experimental conditions that would allow for one to perform the test experiment without a control and still result in information regarding the regulation of gene expression. Since Keeton and Gould teach the vital importance of controlled experimentation, this would require a large amount of unpredictable experimentation. Further, one would be required to carry out additional experimentation to determine how to calculate a ratio from assays that merely determine the presence of a NF-kappaB/Rel protein.

In view of the breadth of the claims and the lack of guidance provided by the specification as well as the unpredictability of the art, the skilled artisan would have required an undue amount of experimentation to make and/or use the claimed invention. Therefore, claims 1-5 are not considered to be fully enabled by the instant specification.

### ***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

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(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 4 and 5 are rejected under 35 U.S.C. 102(b) as being anticipated by Ichiyama et al (Brain Research, Vol. 836, pages 31-37, 1999; see the entire reference). This is a new rejection.

Regarding claim 1, Ichiyama et al teach a method for obtaining information about the capacity or tendency of an oligopeptide of three amino acids to regulate the expression of a gene, comprising the steps of (i) contacting the  $\alpha$ -MSH C-terminal tripeptide,  $\alpha$ -MSH<sub>11-13</sub>, with at least one cell in a C57BL/6 mouse, and (ii) determining the presence of NF-kappaB/Rel protein in a nuclear extract prepared from frozen brain obtained from the treated mouse (e.g., page 31, paragraph bridging columns; pages 32-34, sections 2.1-2.4; Figure 3).

Regarding claim 2, the  $\alpha$ -MSH<sub>11-13</sub> tripeptide is a fragment of the naturally occurring  $\alpha$ -MSH peptide (e.g., page 31, paragraph bridging columns).

Regarding claim 4, the cells of the C57BL/6 mouse are eukaryotic cells (e.g., page 32, section 2.1).

Regarding claim 5, Ichiyama et al teach the additional step of determining the presence of NF-kappaB/Rel protein in a nuclear extract of a brain obtained from a mouse that has not been contacted with the  $\alpha$ -MSH<sub>11-13</sub> tripeptide (e.g., Figure 3). Ichiyama et al teach that NF-kappaB is induced to a greater extent in mice treated with LPS and no peptide as compared to mice treated with LPS and peptide (e.g., Figure 3). Thus, figure 3 is a visual determination of the ratio of NF-kappaB found in mice that have not been treated with  $\alpha$ -MSH<sub>11-13</sub> tripeptide and mice that have been treated with  $\alpha$ -MSH<sub>11-13</sub> tripeptide.

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Claims 1-5 are rejected under 35 U.S.C. 102(b) as being anticipated by Han et al (American Journal of Physiology, Vol. 277, pages C74-C82, July 1999; see the entire reference), as evidenced by Yanaihara et al (US Patent No. 4,330,466; see the entire reference) and GenBank Accession No. NP\_000728 (GI: 4502789, publicly available April 2007). This is a new rejection.

Regarding claim 1, Han et al teach a method for obtaining information about the capacity or tendency of an oligopeptide of 8 amino acids to regulate the expression of a gene, comprising the steps of (i) contacting the cholecystokinin octapeptide (CCK-8) with cells of rat pancreatic acini, and (ii) determining the presence of NF-kappaB/Rel protein by electrophoretic mobility shift assay (EMSA) and Western Blot (e.g., page C75, Pancreatic acini isolation and treatments; page C76, CCK-8 activates NF- $\kappa$ B in pancreatic acini in vitro; Figures 1 and 2).

Regarding claim 2, the CCK-8 peptide of Han et al comprises a sequence corresponding to a fragment of a naturally occurring cholecystokinin peptide (e.g., paragraph bridging pages C74-C75).

Regarding claim 3, the CCK-8 peptide of Han et al comprises an amino acid sequence (i.e., a sequence of two or more amino acids) corresponding to a fragment of human chorionic gonadotropic hormone (hCG). Yanaihara et al is cited only to show that the sequence of the CCK-8 peptide is DYMGWMDF (e.g., column 1, lines 9-30). GenBank Accession No. NP\_000728 is cited only to show that the amino acid sequence MG of the CCK-8 peptide is found at amino acids 15-16 of human chorionic gonadotropic hormone. Thus, the CCK-8 peptide of Ichiyama et al comprises an amino acid sequence (i.e., the sequence MG), which corresponds to a fragment of human chorionic gonadotropic hormone.

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Regarding claim 4, the rat pancreatic acini cells of Han et al are eukaryotic cells (e.g., page C75, Pancreatic acini isolation and treatments).

Regarding claim 5, Han et al teach the abovementioned method further comprising the step of determining the presence of NF-kappaB/Rel protein in cells that have not been contacted with the CCK-8 oligopeptide (e.g., Figures 1 and 2). Figures 1 and 2 are a depiction of the ratio of the NF-kappaB/Rel protein found in the presence and absence of the CCK-8 peptide, and thus Han et al teach the step of determining the ratio of NF-kappaB/Rel protein in cells that have and have not been treated with CCK-8 peptide.

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

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Claims 9 and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Han et al (American Journal of Physiology, Vol. 277, pages C74-C82, July 1999; see the entire reference) in view of Yanaihara et al (US Patent No. 4,330,466; see the entire reference). This is a new rejection.

Han et al teach a method for identifying a signaling molecule comprising a peptide or functional derivative or analogue thereof capable of modulating expression of a gene in a cell, comprising the steps of (i) providing rat pancreatic acinar cells with the CCK-8 octapeptide, and (ii) determining the relative up-regulation of NF-kappaB expression in the cells by electrophoretic mobility shift assay (EMSA) and Western Blot (e.g., page C75, Pancreatic acini isolation and treatments; page C76, CCK-8 activates NF- $\kappa$ B in pancreatic acini in vitro; Figures 1 and 2).

Han et al do not teach the synthesis of the CCK-8 peptide.

Yanaihara et al teach the synthesis of CCK-8 octapeptide (e.g., column 1, lines 9-30; Examples 1 and 3). Yanaihara et al teach that it is possible to obtain highly effective CCK-8 in a good yield using the disclosed process, and thus the process is extremely advantageous over industrial processes (e.g., column 3, lines 7-11).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method of testing the CCK-8 octapeptide of Han et al to include the synthesis of the CCK-8 octapeptide taught by Yanaihara et al because Han et al teach it is within the ordinary skill in the art to use the CCK-8 octapeptide and Yanaihara et al teach a method of making the CCK-8 octapeptide.



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One would have been motivated to make such a modification in order to receive the expected benefit of providing highly effective CCK-8 at a good yield as taught by Yanaihara et al. One would have been motivated to produce CCK-8 to repeat the experiment taught by Han et al or to conduct further studies with the CCK-8 peptide. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

***Response to Arguments - 35 USC § 103***

The rejection of claims 1-5 under 35 U.S.C. 103(a) as being unpatentable over Lunardi-Iksandar et al (U.S. Patent No. 5,677,275) in view of Matsushima et al (U.S. Patent No. 5,981,486) has been withdrawn in view of Applicant's amendment to the claims in the reply filed 6/30/2006. Lunardi-Iksander and Matsushima, alone or in combination, do not specifically teach or suggest contacting an oligopeptide of at most 9 amino acids long with a cell.

***Conclusion***

No claims are allowed.


Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Dunston whose telephone number is 571-272-2916. The examiner can normally be reached on M-F, 9 am to 5 pm.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached at 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Jennifer Dunston, Ph.D.  
Examiner  
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A handwritten signature in black ink, appearing to read "Jennifer Dunston", written in a cursive style.

/JD/